This amendment is accompanied by (1) a version of the replacement claims that has been marked up to show all changes relative to the previous version of the claims and (2) a clean copy of all pending claims.

REMARKS

Claims 1-3, 5-6, 8-31, and 33-44 are pending in the above-identified application. Claims 9, 22, and 42 stand rejected under 35 U.S.C. §112, first paragraph. Claims 12, 25, 28, 36-37, and 38 stand rejected under 35 U.S.C. §112, second paragraph. Claims 43-44 stand rejected under 37 C.F.R. §1.75. Claims 15-16, 19-21, 23-25, 38, 39, and 43-44 stand rejected under 35 U.S.C. §102(b). Claims 1-3, 5-6, 8-14, 17-18, 22-31, and 34-44 stand rejected under 35 U.S.C. §103(a). With this response, claims 20, 43, and 44 have been cancelled, and claims 1, 9, 13, 14, 15, 22, 26, 27, 28, 33, 37, 40, 41, and 42 have been amended. Reconsideration of the claims as amended is respectfully requested.

I. Applicants' Invention.

The present invention is directed to an immunological adjuvant composition useful for enhancing the immune response against antigens. The adjuvant composition includes a first adjuvant comprised of an amorphous calcium phosphate formulated as a hardenable, injectable paste having a solids content of greater than or equal to 40 wt%.

The adjuvant composition alternatively includes as a first adjuvant an injectable calcium phosphate composition, comprised of an amorphous calcium phosphate and a second calcium phosphate, that is capable of hardening at body temperature. The injectability and hardening ability of the adjuvant improves adjuvant and antigen delivery.

The adjuvant composition alternatively includes a first adjuvant comprising a calcium phosphate paste, which is comprised of an amorphous calcium phosphate and a second calcium phosphate, and a second adjuvant, wherein the first and second adjuvant are selected to elicit an immunological response of a specific cell type. The use of a second adjuvant augments the effect observed in the primary adjuvant, either by enhancing a response in the cell type targeted by the first adjuvant or eliciting an immune response in a different cell type.

II. Claim Amendments.

Support for claims 1, 13, and 14 as amended is found at page 43, lines 14 to 17. Support for claims 15, 26, 27, and 28 as amended is found at page 11, lines 5-11; United States Patent No. 5,683,461, incorporated by reference into the current application at page 11, line 10, teaches the preparation of pastes comprised of an amorphous calcium phosphate and a second calcium phosphate. Support for claim 37 as amended is found at page 37, line 19 to page 38, line 7 and at page 43, lines 14 to 17.

III. Rejection of Claims Under 35 U.S.C. §112, First Paragraph.

Claims 9, 22, and 42 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not reasonably enabled by the specification. Specifically, the Examiner contends that the selection of "polymers" for use as second adjuvants in the claimed compositions and effective delivery of compositions including these polymers are not enabled. The term "polymer" has been canceled from claims 9, 22, 33, and 42, thereby obviating the rejection.

IV. Rejection of Claims Under 35 U.S.C. §112, Second Paragraph.

Claims 12, 25, 28, 36-37, and 38 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

The Examiner rejected claim 37 on the grounds that the recitation "the first adjuvant" lacks antecedent basis. Claim 37 has been amended to provide the requisite antecedent basis, and Applicants, therefore, believe this rejection is overcome.

The Examiner rejected claims 28, 37, and 38 on the grounds that the phrase "elicit a response of a specific immune cell type" is vague. Applicants believe the Examiner's reference to claim 38 is in error, as that claim does not contain the cited language. Applicants have amended claims 28 and 37 to provide that the adjuvants are selected "so as to elicit an immune response from targeted cells or cell types." This amended language clarifies that adjuvant selection depends upon the cells to be manipulated. The specification explains that "manipulation of specific immune response components" may be affected by, among other things, adjuvant combinations (p. 26, l. 10-13). Additionally, Example 18, Table 1, provides guidance for selecting an appropriate adjuvant combination based on the desired immune response. Thus, Applicants believe this rejection is overcome and may be withdrawn.

The Examiner rejected claims 12, 25, and 36 on the grounds that the terms "RANTES," "Fas ligand," "OSM," "LIF," "4-1BBL," "MCP-1," and "MIP" are indefinite and the specification fails to teach the identity of the corresponding cytokines. These cytokine abbreviations are well known and readily understood by those of skill in the art. Biology reference books and easily-accessible Internet resources use the recited terms, indicating they are commonly used in the field. To assist the Examiner, however, Applicants provide the following additional explanations for these terms:

- RANTES: a member of the interleukin-8 superfamily of cytokines. This cytokine is a selective chemoattractant for memory T lymphocytes and monocytes (*Stedman's Medical Dictionary*, p. 1496 (M. Spraycar ed., 26th edition 1995)) (copy attached);
- Fas ligand: (also known as CD95 ligand) a type-II membrane protein expressed predominantly on natural killer cells and activated T-cells (http://biochem.roche.com/apoptosis/fasl.htm) (copy attached, downloaded from website on March 21, 2002);
- OSM: oncostatin M (http://cytokine.medic.kumamoto-u.ac.jp/CFC/IL-6/LIF-OSM.html) (copy attached; downloaded from website on March 22, 2002);
- LIF: leukemia inhibition factor (Alberts et al. *Molecular Biology of the Cell*, p. 1059 (3d. edition 1994)) (copy attached);
- 4-1BBL: definition and source to be provided by Etex;
- MCP-1: monocyte chemoattractant protein-1 (*Stedman's Medical Dictionary*, p. 1071 (M. Spraycar ed., 26th edition 1995)) (copy attached); and
- MIP: macrophage inflammatory protein (*Stedman's Medical Dictionary*, p. 1119 (M. Spraycar ed., 26th edition 1995)) (copy attached)

Given that numerous literature and internet references use the recited terms, as demonstrated by the explanatory information provided above, Applicants submit that the recited cytokine terms "RANTES," "Fas-l," "OSM," "LIF," "4-1BBL," "MCP-1," and "MIP" are well known to those of skill in the art. Therefore, Applicants respectfully request the withdrawal of the Section 112, second paragraph, rejection of claims 12, 25, and 36.

V. Rejection of Claims Under 37 C.F.R. §1.75.

Claims 43 and 44 stand rejected under 37 C.F.R. §1.75 as being substantial duplicates of claim 23. With this response, claims 43 and 44 have been cancelled, thereby obviating the rejection.

VI. Rejection of Claims Under 35 U.S.C. §102(b).

A. Anticipation By Towey et al.

Claims 15-16, 19-21, 23, 38, 39, and 43-44 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Towey *et al.* (U.S. Patent No. 2,967,802). The rejected claims are directed to immunological adjuvants including an injectable calcium phosphate paste capable of hardening at body temperature wherein the paste includes amorphous calcium phosphate and a second calcium phosphate. The Examiner suggests that Towey meets all of the limitations of the instant claims. For the reasons provided below, Applicant respectfully disagrees.

Applicants have reviewed Towey and found no teaching or suggestion of the claimed calcium phosphate pastes. Towey does not teach the use of a "hardenable, injectable paste comprised of an amorphous calcium phosphate and a second calcium phosphate," as recited in amended claim 15. Towey teaches the use of calcium phosphate gels with a solids content of less than or equal to 15 wt% (col. 2, l. 35-38 and col. 3, l. 15-17). The solids (of undisclosed composition) are used as the sole calcium phosphate component of the gel. There is no teaching of a two component paste comprising amorphous calcium phosphate and a second calcium phosphate. Towey, therefore, fails to teach all of the limitations of the instant claims.

Moreover, Towey fails to disclose immunological adjuvants comprised of calcium phosphate compositions capable of hardening at body temperature, as recited in claim 15. The

passages referenced in the Office Action disclose only low solid content calcium phosphate gels. It is not proper to equate low solids content gels with the instantly claimed hardenable pastes. In fact, the low solids content of the gels disclosed by Towey renders them incapable of hardening at body temperature (col. 2, l. 35-38 and col. 3, l. 15-17). Thus, Towey fails to disclose the use of hardenable calcium phosphate pastes in an adjuvant composition.

B. Anticipation By Relyveld.

Claims 15-16, 19-20, 23-25, 27, 38, 39, and 43-44 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Relyveld (U.S. Patent No. 4,016,252). The Office Action suggests that Relyveld's disclosed vaccines comprised of calcium phosphate gels contain all of the limitations of Applicants' claimed compositions. The Office Action further suggests that Relyveld's disclosed coadministration of antigens and calcium phosphate gels to increase antigen immunogenicity anticipates Applicants' claimed adjuvant compositions. Applicant respectfully disagrees.

The teachings of Relyveld suffer from the same deficiencies as those of Towey, discussed above, in that they disclose only non-hardenable, single-component calcium phosphate gels. Claims 15 and 27 as amended disclose a "hardenable, injectable paste comprised of an amorphous calcium phosphate and a second calcium phosphate". There is no teaching or suggestion in Relyveld of a two-component paste comprising an amorphous calcium phosphate and a second calcium phosphate. Furthermore, the low solids content of the calcium phosphate gels ($\leq$ 3.3 wt%; col. 5, 1. 38-41 and col. 9, 1. 24-31) renders them incapable of hardening at body temperature, in contrast to Applicants' claimed pastes.

C. *Functional limitations must be considered.*

With respect to both Towey and Relyveld, the Office Action suggests that the claimed pastes' ability to harden at body temperature is a functional limitation that "does not further limit components of composition" (Office Action, May 22, 2001, p. 6). Applicants respectfully disagree. It is a well-settled proposition of law that effect must be given to all claim limitations. The inclusion of two calcium phosphate sources in the claimed pastes contributes to their ability to harden at body temperature. These features of the paste are not "functional" and must be given full weight. When given effect, these features distinguish Applicants' pastes from the Relyveld compositions referenced by the Examiner. Towey and Relyveld does not teach or suggest the combination of two calcium phosphate components to produce a calcium phosphate paste or the use of such two-component pastes as vaccine adjuvants.

In summary, Applicants submit that the amended claims are distinguished over Towey and Relyveld, and the Section 102(b) rejection may now be withdrawn.

VII. Rejection of Claims Under 35 U.S.C. §103(a).

Claims 1-3, 5-6, 8, 10-14, 17-18, 23-27, 39, and 43-44 stand rejected under 35 U.S.C. §103(a) as unpatentable over Relyveld (U.S. Patent No. 4,016,252), in view of Amerongen *et al.* (U.S. Patent No. 5,443,832) and Constanz *et al.* (U.S. Patent No. 5,782,971).

Claims 9, 22, 28-31, 33, 34-38, and 40-42 stand rejected under 35 U.S.C. §103(a) as unpatentable over Relyveld (U.S. Patent No. 4,016,252), in view of Amerongen *et al.* (U.S. Patent No. 5,443,832) and Constanz *et al.* (U.S. Patent No. 5,782,971), and further in view of Gupta *et al.* (Vaccine Design, Ch. 8, pp. 229-248 (1995)) or Kossovsky *et al.* (U.S. Patent No. 5,462,751).

A. Rejection Of Claims Directed To Hardenable, Injectable Amorphous Calcium Phosphate Pastes.

Claims 1-3, 5-6, 8, 10-14, 17-18, 23-27, 39, and 43-44 stand rejected as unpatentable over Relyveld (U.S. Patent No. 4,016,252), in view of Amerongen *et al.* (U.S. Patent No. 5,443,832) and Constanz *et al.* (U.S. Patent No. 5,782,971). The rejected claims are directed to adjuvant compositions comprised of hardenable, injectable amorphous calcium phosphate pastes having at least 40 wt% solids content and/or a two-component calcium phosphate composition. The Examiner suggests that it would have been obvious to one skilled in the art to modify the solids content of known calcium phosphate adjuvant compositions so as to formulate Applicants' hardenable, injectable calcium phosphate pastes. Specifically, the Examiner suggests that the combination of (1) Relyveld's teaching of calcium phosphate gels as adjuvants; (2) Amerongen's teaching of calcium phosphate particles in amounts higher than 40% as immune response elicitors; and (3) Constanz's teaching of hardenable, amorphous calcium phosphate pastes render Applicants' claimed pastes obvious. Applicants submit these references are insufficient to sustain the Section 103(a) rejection for the reasons provided below.

1. <u>Relyveld and Amerongen fail to teach calcium phosphate compositions having 40 wt% solids contents or a two-component calcium phosphate composition sufficient to produce hardenable, injectable calcium phosphate pastes.</u>

The rejected claims are directed to calcium phosphate adjuvant compositions having a solids content of greater than or equal to 40 wt% and/or to a two-component calcium phosphate paste comprising amorphous calcium phosphate and a second calcium phosphate. The high solids content and/or two-component formulation of the paste contributes to the ability of Applicants' compositions to form pastes that harden at body temperature. In contrast, the calcium phosphate compositions of Relyveld and Amerongen are one-component systems that

lack comparable solids contents and are, consequently, not hardenable. In fact, the relevant prior art consistently teaches away from the hardenable adjuvant compositions claimed by Applicants.

As discussed above, argued in previous Responses (Response to Office Action, June 16, 2000), and admitted by the Examiner (Paper No. 15, p. 7), Relyveld "fails to show the instant 40 wt% solids in his composition", as recited in independent claims 1, 13 and 14. As discussed above, in Section VI(B), Relyveld also fails to teach hardenable calcium phosphate pastes comprised of amorphous calcium phosphate and a second calcium phosphate, as recited in independent claims 15 and 26-28. Thus, Relyveld teaches away from calcium phosphate compositions having the recited solids content or composition sufficient to permit hardening.

A correct reading of Amerongen likewise fails to suggest calcium phosphate compositions sufficient to yield Applicants' hardenable pastes. While the Office Action states that Amerongen teaches calcium phosphate particles in amounts greater than 40 wt% (Paper No. 15, p. 7), Applicant respectfully disagrees. The referenced portion of Amerongen teaches 1mg of hydroxyapatite in 200µl of water (col. 6, l. 26-34), which is equivalent to 0.001g of hydroxyapatite in 0.2mL of water, and, assuming a density of 1g/mL for water, yields a solids content of about 0.5 wt%. Applicants have reviewed Amerongen and found no teaching of calcium phosphate particles in amounts greater than 0.5 wt%. Amerongen, therefore, also teaches away from compositions capable of forming the hardenable calcium phosphate pastes claimed by Applicants, as recited in claims 1, 13 and 14.

Amerongen also fails to teach or suggest a hardenable calcium phosphate paste comprised of amorphous calcium phosphate and a second calcium phosphate, as recited in independent claims 15 and 26-28. Amerongen teaches hydroxylated calcium phosphate particulate, specifically hydroxyapatite, as a carrier for antigens to be applied to mucosal

surfaces (col. 2, l. 39-41). There is no suggestion of a two-component calcium phosphate paste comprising amorphous calcium phosphate and a second calcium phosphate. The Office Action itself noted Amerongen's failure to teach paste compositions in his most recent Office Action, stating that "Amerongen fails to teach their compositions in an injectable paste form" (Office Action, May 22, 2001, p. 7). Thus, Amerongen, like Relyveld, fails to teach or suggest calcium phosphate compositions having the solids content or the composition of the claimed invention.

Moreover, neither Relyveld nor Amerongen provides the slightest motivation to increase the solids content of their disclosed gels so as to produce Applicants' claimed hardenable, injectable pastes. In fact, the prior art consistently teaches the advantages of using calcium phosphate gels with low solids contents as vaccine adjuvants, a teaching premised on the perceived importance of the gels' large surface area for antigen adsorption (Goto *et al.*, *Vaccine* 15(12-13):1364-71 (1997); Gupta *et al.*, *Vaccine Design*, Ch. 8, pp. 229-48 (1995); Kato *et al.*, *Microbiol. Immunol.* 38(7):543-48 (1994); Goto *et al.*, *Vaccine* 11(9):914-18 (1993); Gupta *et al.*, *Vaccine* 11(3):293-306 (1993); E.H. Relyveld, *Dev. Biol. Stand.* 65:131-36 (1986)). Applicants' use of high solids content, two-component compositions to promote adjuvant hardening is, therefore, a dramatic departure from the vaccine art's consistent prior teachings that adjuvant hardening was undesirable. This strong teaching of non-hardening adjuvant gels leaves the vaccine prior art utterly devoid of references suggesting the use of hardenable, injectable calcium phosphate pastes as vaccine adjuvants. The Office Action suggests, however, that the teachings of Constantz can fill this void. Applicants respectfully disagree.

2. There is no motivation to combine Constantz with Relyveld and Amerongen.

To establish obviousness by combining references, the law is unequivocal that one must find motivation and suggestion in the relevant prior at to combine that art into something which

makes the invention obvious. *Pro-Mold & Tool Co. v. Great Lakes Plastics*, 75 F.3d 1568, 1573 (Fed. Cir. 1996); *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 934 (Fed. Cir. 1990), *cert. denied* 111 S.Ct. 296 (1990). Obviousness cannot be established by combining teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. *In re Jones*, 21 U.S.P.Q.2d 1941, 1944 (Fed. Cir. 1992). The Federal Circuit has admonished that requiring the suggestion or motivation to combine is the safeguard against using a claim as a blueprint to pick and choose from the prior art using hindsight to reconstruct a claim. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985).

Constantz teaches calcium phosphate cements for bone remodeling. The cements include tetracalcium phosphate (55-75 wt%) or tricalcium phosphate (70-85 wt%), calcium carbonate (2-18 wt%), a phosphoric acid source (1-25 wt%), and a small amount (<15 wt%) of amorphous calcium phosphate (col. 4, l. 23 – col. 5, l. 3). The reference discloses that various combinations of the above ingredients result in cements of varying setting times. The specification discusses the potential application of the cement in bone or connective tissue related applications or as a vehicle for drug deliver (col. 6, l. 56-62). There is no discussion of any immunogenic properties of the material. While Constanz teaches amorphous calcium phosphate compositions capable of setting in vivo (col. 1, l. 24-31 and col. 6, l. 40-47), these hardenable compositions are never taught as vaccine adjuvants, a deficiency recognized in the most recent Office Action (Office Action, p. 8, "Constantz, however, fails to disclose vaccine formulations").

While both Relyveld and Amerongen disclose calcium phosphate adjuvant compositions, neither so much as even hints at the use of hardenable calcium phosphate compositions, as discussed above. These references are representative of the prior art in the vaccine field at the time the instant application was filed, which overwhelmingly stressed the importance and

desirability of high-liquid content, flowable gel adjuvant compositions (*see, e.g.,* Gupta *et al. Vaccine Design*, Ch. 8, pp. 229-48 (1995) at p. 240). Thus, one of ordinary skill in the art would not look to bone remodeling materials that are highly viscous and that harden into a cement as a source for adjuvant materials. There is no rationale or stated basis in the prior art to expect that the hardenable calcium phosphate composition of Constantz would have adjuvant properties.

In conclusion, none of the cited references contain the suggestion the law requires for their combination. The Examiner's combination of the distinct teachings of Relyveld and Amerongen with those of Constanz amounts to nothing more than impermissible hindsight reconstruction of Applicants' claims to hardenable calcium phosphate adjuvant compositions. Accordingly, it is submitted that Constanz is insufficient to remedy the shortcomings of Relyveld and Amerongen, and the Section 103(a) rejection of claims 1-3, 5-6, 8, 10-14, 23-27, 39, and 43-44 should be withdrawn.

B. Rejection Of Claims Directed To Adjuvant Compositions Comprising Calcium Phosphate And A Second Adjuvant.

Claims 9, 22, 28-31, 33, 34-38, and 40-42 stand rejected under 35 U.S.C. §103(a) as unpatentable over Relyveld (U.S. Patent No. 4,016,252), in view of Amerongen *et al.* (U.S. Patent No. 5,443,832) and Constanz *et al.* (U.S. Patent No. 5,782,971), and further in view of Gupta *et al.* (Vaccine Design, Ch. 8, pp. 229-248 (1995)) or Kossovsky *et al.* (U.S. Patent No. 5,462,751). These claims are directed to adjuvant compositions comprising the claimed hardenable, injectable amorphous calcium phosphate pastes and a second adjuvant. The Office Action suggests it would have been obvious to one of ordinary skill in the art to combine the teachings of Relyveld, Amerongen, and Constanz so as to create a hardenable, injectable calcium phosphate formulation, as discussed above in Section VII(A), and to further incorporate a second

adjuvant as taught by Gupta or Kossovsky. For the reasons provided above these claims are patentable. The newly cited references do not provide the requisite teachings found lacking in the primary references.

Gupta teaches calcium phosphate gels as alternatives to aluminum adjuvants in childhood vaccines (p. 239). Antigen may be adsorbed onto the calcium phosphate gels via in situ preparation of the gel in the presence of antigens or adsorption onto the preformed gel (p. 239). Applicants' review of Gupta found therein no suggestion that the disclosed gels' adjuvanticity would be improved by modifying the gels' solids content or including a second calcium phosphate component so as to produce a hardenable paste. This reading is supported by the Office Action itself, noting that Gupta "does not teach various percentages of solid amount" (Office Action, May 22, 2001, p. 9).

Kossovsky teaches crystalline calcium phosphate particles (brushite) suspended in a carbohydrate coating solution, which enhances binding of biologically active vaccine agents to the core particles (col. 4, l. 1-4 and col. 5, l. 7). Following suspension in the coating solution, the core particles may be separated and redispersed in a solution containing biologically active agents or may be left in solution for further treatment (col. 7, l. 45-50). Like Gupta, Kossovsky fails to suggest modification of the compositions' solids content or inclusion of a second calcium phosphate component so as to produce hardenable calcium phosphate adjuvants. This critical Section 103(a) shortcoming was recognized by the most recent Office Action (p. 10: Kossovsky "fails to specifically teach a hardenable paste formulation for injection").

Thus, alone and in view of the primary references, neither Gupta nor Kossovsky teaches hardenable, injectable calcium phosphate pastes, a limitation included in each of the rejected claims. Given these crucial deficiencies in Gupta and Kossovsky, their disclosure of calcium

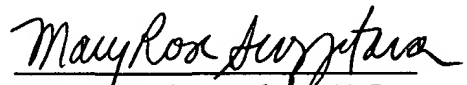
phosphate compositions with second adjuvants is insufficient to sustain the Examiner's Section 103(a) rejection. Applicants' claimed hardenable, injectable amorphous calcium phosphate adjuvant compositions clearly represent a non-obvious departure from the teachings of the prior art. Applicants, therefore, respectfully request that the Section 103(a) rejection of claims 9, 22, 28-31, 33, 34-38, and 40-42 be withdrawn.

VIII. Conclusion.

For the foregoing reasons, it is submitted that claims 1-3, 5-6, 8-31, and 33-44 are patentable over the cited prior art. A favorable notice to that effect is requested.

Respectfully submitted,

Date: May 21, 2002



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Marked-up Claims Showing All Changes
Relative to the Previous Version of the Claims

1. An immunological adjuvant composition useful for enhancing the immune response against antigens, comprising:

a first adjuvant, wherein said first adjuvant comprises amorphous calcium phosphate formulated as a[~~n~~] hardenable, injectable paste having a solids content of greater than or equal to 40 wt%.

9. A composition of claim 8, wherein said second adjuvant is selected from: muramyl dipeptide, aluminum hydroxide, aluminum phosphate, hydroxyapatite, Incomplete Freund's Adjuvant, and Complete Freund's Adjuvant [~~and polymers~~].

13. A method for stimulating an immune response in a mammal, said method comprising:

administering to the mammal a composition comprising amorphous calcium phosphate formulated as a[~~n~~] hardenable, injectable paste having a solids content of greater than or equal to 40 wt%.

14. A method for increasing immunogenicity of an antigen in a mammal, said method comprising:

co-administering both an antigen and a composition comprising amorphous calcium phosphate formulated as a[~~n~~] hardenable, injectable paste having a solids content of greater than or equal to 40 wt%.

15. An immunological adjuvant composition useful for enhancing the immune response against antigens, comprising:

a first adjuvant comprised of an injectable calcium phosphate paste capable of hardening at body temperature, wherein said paste is comprised of an amorphous calcium phosphate and a second calcium phosphate.

22. A composition of claim 21, wherein said second adjuvant is selected from: muramyl dipeptide, aluminum hydroxide, aluminum phosphate, hydroxyapatite, Incomplete Freund's Adjuvant, and Complete Freund's Adjuvant [~~and polymers~~].

26. A method for stimulating an immune response in a mammal, said method comprising:

administering to the mammal an injectable [~~paste comprised of a hardenable~~] calcium phosphate paste comprised of [~~a hardenable calcium phosphate composition~~] an amorphous calcium phosphate and a second calcium phosphate, wherein said [~~the~~] paste hardens at body temperature and stimulates an immune response in the host.

27. A method for increasing immunogenicity of an antigen in a mammal, said method comprising:

co-administering both the antigen and a composition comprising an injectable calcium phosphate paste capable of hardening at body temperature, wherein said paste is comprised of an amorphous calcium phosphate and a second calcium phosphate.

28. An immunological adjuvant composition useful for enhancing the immune response against antigens, comprising:

a first adjuvant, wherein said first adjuvant [~~comprises~~] is a hardenable, injectable calcium phosphate paste comprised of an amorphous calcium phosphate and a second calcium phosphate; and

a second adjuvant, wherein the first and second adjuvant are selected so as to elicit an immune response from targeted cells or cell types [~~of a specific immune cell type~~].

33. A composition of claim 9, 22, or 28, wherein [~~said~~] the second adjuvant is selected from the group consisting of a second calcium phosphate, muramyl dipeptide, aluminum

hydroxide, aluminum phosphate, hydroxyapatite, Incomplete Freund's Adjuvant, and Complete Freund's Adjuvant [~~and polymers~~].

37. A method for stimulating an immune response in a mammal, said method comprising administering to the mammal a first adjuvant composition comprising a hardenable, injectable amorphous calcium phosphate paste and a second adjuvant, wherein the first and second adjuvants are selected so as to elicit an immune response from targeted cells or cell types [~~of a specific immune cell type~~].

40. The composition of claim 28, wherein the first and second adjuvants are selected so as to elicit an immune [~~immunological~~] response from cells of the same type [~~in the same immune cell type~~].

41.The composition of claim 28, wherein the first and second adjuvants are selected so as to elicit an immune [~~immunological~~] response from cells of different types [~~in different immune cell types~~].

42. The method of claim 37, wherein said second adjuvant is selected from the group consisting of a second calcium phosphate, muramyl peptide, aluminum hydroxide, aluminum phosphate, hydroxyapatite, Incomplete Freund's Adjuvant, and Complete Freund's Adjuvant [~~and polymers~~].